FORMULATION DEVELOPMENT AND IN-VITRO EVALUATION OF POTASSIUM CHLORIDE EXTENDED RELEASE TABLETS

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1. INTRODUCTION

1.1 TABLETS:

This chapter deals first with the main aspects of tablet dosage forms before addressing the process of manufacture and testing of these most popular drug delivery systems. Per oral tablets occupy the broadest and the most significant place among all pharmaceutical dosage forms. Taking one or two tablets a day with a glass of water is the easiest and the most acceptable way of administration of a drug to a patient. William Brockedon patented the first tablet press in 1843 to compress potash and lime tablets, thus paving the way for the modern manufacture of tablets. Drugs are administered in a wide variety of doses. Tablets of L-thyroxine, for example, may contain as low as 25 mg drug. On the other hand, amoxicillin/clavulanicacid tablets contain 1 g of actives per tablet. These two extremes cover a 10,000-fold range of drug content. Tablets may be made in different sizes and shapes, and the drug substance may comprise 0.1% to 90% of a tablet bulk. From the point of view of ease of manufacture, tablet production, compared with other dosage forms, provides the highest output per manufacturing hour, and is the most economical, especially if one considers modern manufacturing methods involving processes suchas the direct compression (DC) or fluidized-bed granulation. While tabletting may appear from what has been said to be a facile process, it is often far from straightforward. Drug molecules show various differences in physical and chemical properties. These include differences in their crystalline structure, particle size, water solubility, dose, and sensitivity to hydrolysis or oxidation, topics discussed elsewhere in this book. Hence, every drug molecule must be treated as a unique entity for formulation. Drugs synthesized in the last 30 years have been increasingly showing limited water solubility, poor flow and compression properties, and sensitivity to moisture and heat. Preparing a tablet dosage form from such molecules is a

challenge, since the market demands easy and cost-effective manufacturing, an acceptable dissolution rate, and of course high bioavailability, and mechanically strong tablets that resist fracture during packaging,

Transport and ultimately in patient use. Further more, the tablets must fulfill the requirements for bioavailability and, eventually, bioequivalence. When considering all these factors, designing and manufacturing a successful tablet requires optimization of the formulation and processing parameters, which can be achieved by the application of a thorough knowledge of excipients, and the subsequent selection of the most suitable manufacturing process.[1]

1.1 a) ADVANTAGES OF TABLETS:

- ✓ Tablets are the unit dosage form having greatest capabilities of all oral dosage form for the dose precision and least content variability.
- ✓ Their cost is lower of all oral dosage forms.
- ✓ They are lightest and the most compact of all oral dosage forms.
- ✓ Tablets are easiest and cheapest for packaging and transportation.
- ✓ They lend themselves to certain special release profile products such as enteric or delayed release products.
- ✓ Tablets are better for large -scale production than other unit oral forms.
- ✓ They have the best-combined properties of chemical, mechanical, microbiological stability of all oral forms.
- ✓ Tablets are easiest and cheapest for packaging and transportation.[2]

1.1 b) LIMITATIONS OF THE TABLETS:

- ✓ Some drugs resist compression in to dense particles, owing to their amorphous nature or flocculent, low-density character.
- ✓ Drugs with poor wetting slow dissolution properties, intermediate to large dosages, optimum absorption high in the GIT, or any combination of these features difficult to formulate.
- ✓ Bitter tasting drugs with an objectionable odor, or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation or entrapment prior to compression.

1.2 TYPES OF TABLETS AND TABLET DESIGN:

Tablet design is based on the experience and knowledge of excipients, which are materials serving the purpose of making a good tablet when combined with a drug. The mechanical and chemical properties of excipients have the utmost importance, and the area is closely related to materials engineering as well as pharmacy. Expected properties of a modern tablet include mechanical strength suitable for coating, packaging, and transportation; an optimum size, shape, and color for identification; ease of swallowing; and, finally, fulfilling the pharmacopoeial requirements for drug content and release rates as well as stability and bioavailability. Some of the pharmaceutical tablet types based on the way of administration or presentation to the patient are listed below:

- ➢ Simple uncoated tablets
- ➢ Coated tablets
- ➢ Effervescent tablets
- ➢ Buccal and sublingual tablets

- Chewable tablets
- Multilayered tablets
- Sugarcoated tablets
- Fast-disintegrating tablets
- Vaginal tablets
- Modified release tablets
- Extended release tablets

a) Simple Uncoated Tablets

The simplest form of a pharmaceutical tablet consists of a combination of a drug and some functional excipients compressed directly. This tablet should be formed by compression without difficulty using binders, disintegrants, and lubricants, and when used by a patient, it should disintegrate in the stomach and should of course be bioavailable. Such simple tablets are manufactured by mixing the drug and excipients in a V-shaped mixer and are compressed in a tablet press using dies and punches of suitable size.

b) Film-Coated Tablets

A tablet can be coated with a polymer film to provide greater ease of swallowing, protection against light or moisture, protection of the drug from gastric acidity, and modification or control of drug release rate. Identification of a formulation by color or logo is extremely important today not only for patient safety but also because of the problem of counterfeiting. Polymers and processes are available to achieve all of these properties.

c) Effervescent Tablets

Effervescent tablets are designed to dissolve or disperse quickly in water as a result of the release of carbon dioxide from the reaction between sodium bicarbonate and citric acid in the formulation. Such tablets are generally the largest tablets in terms of size and weight, with diameters up to 3 cm and weights of the order of 4 to 5 g. Although they are called tablets, the mode of administration is naturally indirect; the patients take the drug solution or suspension after dispersal. Their manufacture may require a low humidity environment, special tablet presses, and specialized lubrication for tablet ejection.

d) Buccal and Sublingual Tablets

These special tablets are designed for fast and complete drug action through dissolution in the buccal cavity or placement sublingually. As a result, the first pass effect may be avoided. Buccal tablets are used for hormone replacement therapy, for example, with methyl testosterone; sublingual tablets are frequently used for the delivery of isosorbidedinitrate and nitroglycerin.

e) Chewable Tablets

Sometimes a tablet is designed in such a way that it is chewable. This results in its disintegration. Chewable tablets have some advantages, among them being that a large dose of a drug can be formulated, since the tablets are not swallowed whole. Children can be convinced to take such medication, no water is required for administration, and the disintegration step for a tablet is actively achieved in the mouth before it dissolves in the gastric medium. Pediatric multivitamin or mineral formulas, aspirin, vitamin C 1000 mg,and vitamin A 50,000 units are usually formulated as chewable tablets.

f) Multilayered Tablets

Tablets can be designed and manufactured to have separate layers or a core tablet inside a tablet. In this way, two or more drugs can be kept separate in a single tablet. Such complicated systems have found limited applications over the years in the pharmaceutical industry, but there is a revival of interest in the use of combination dosage forms for thetreatment of diseases such as AIDS, where multiple drugs are administered each day. Tablet presses with two or three hoppers are available for the purpose of preparing multilayered dose forms. These include the Colton 232, the KilianPrescoter, and the ManestyDryCota machines. Recently, an excellent application potential was reported for compression coating, namely, the colonic delivery of drugs using a pectin-hydroxypropyl methyl cellulose (HPMC) combination, which was successful for the delivery of 5-aminosalycylic acid (5-ASA), and also for peptides such as nisin. This type of drug delivery system requires compression-coating equipment for mass production since a 100- mg core tablet containing the drug is surrounded by a pectin-HPMC mixture.

g) Sugarcoated Tablets (Dragees)

Before the development of film-coating processes, the major coating material was a sugarcoat. Tablets were sugarcoated for the very same reasons as film coating. These tablet types generally start with a seed or core tablet that contains the drug, and the resultant coating process is a lengthy one using simple syrup, shellac, and talc, several layers of which are deposited onto the core tablet. Usually, a weight increase of as muchas 100% to 300% is considered normal.

h) Fast-Disintegrating Tablets

This type of tablet is the newest addition to the family of tablets. The main reason for the development of such tablets is the potential for administration of small doses to the elderly or children who have difficulties in swallowing intact tablets. A tablet is administered by placing it on a spoon and adding some water, in two to four seconds the tablet completely disintegrates to granules that can be swallowed easily. Fast-disintegrating tablets are not only made out of special granules but can also be compressed using coated spherical pellets such as enteric-coated omeprazole pellets.

i) Vaginal Tablets

Tablets are made to be used for insertion into the vagina for treatment of local infections or hormone replacement therapy. For instance, ornidazole and micanazole nitrate combination and estradiol hemihydrate tablets are formulated as vaginal tablets. These tablets release the drugs slowly in 20 to 30 minutes.

j) Modified-release tablets:

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of modified release drug delivery systems. The modified-release delivery systems may be divided conveniently into four categories:

1. Delayed release
2. Sustained release
3. Site-specific targeting
4. Receptor targeting

i) Delayed release system: Delayed-release systems are those that use repetitive, intermittent dosing of a drug from one or more immediate-release units incorporated into a single dosage form. Examples of delayed-release systems include repeat-action tablets and capsules, and enteric-coated tablets where timed release is achieved by a barrier coating.

ii) Sustained release system: During the past few years, conventional dosage forms of drugs are rapidly being replaced by the new and the novel drug delivery systems. Amongst, these the controlled release/sustained release dosage forms have become extremely popular in modern therapeutics. The basic rationale for sustained release drug delivery is to alter the pharmacokinetics and pharmacodynamics of drugs by using novel drug delivery systems or by modifying the molecular structure or physiological parameters inherent in a selected route of administration. It is desirable that the duration of drug action becomes more a design property of a rate controlled dosage form and less or not at all a property of the drug molecule's inherent kinetic properties. Thus, optimal design of a sustained/ controlled release system necessitates a thorough understanding of the pharmacokinetics and pharmacodynamics of the drug. When the drug is administered in a conventional dosage form, it results in a fluctuation of drug concentration at the site of action (peak and valley pattern) and therefore in systemic circulation and tissue compartment.

- **Advantages of sustained release drug delivery:**

Following are the potential advantages of sustained release products

- Decreased local and systemic side effects reduced gastrointestinal irritation.
- Better drug utilization reduction in total amount of drug used.

- Improved efficiency in treatment, optimized therapy, more uniform blood concentration.
- Reduction in fluctuation in drug level and hence more uniform pharmacological response, cure of control of condition more promptly, less reduction in drug activity with chronic use.
- Method by which sustained release is achieved can improve the bioavailability of some drugs e.g. drugs susceptible to enzymatic inactivation can be protected by encapsulation in polymer systems suitable for sustained release.
- Improved patient compliance, less frequent dosing, reduced night-time dosing, reduced patient care time. The importance of patient compliance in successful drug therapy is well recognized. It has been found that there is an inverse relationship between the number of dosages per day and the compliance rate.
- Although the initial unit cost of sustained release products is usually greater than that of conventional dosage forms because of the special nature of these products, the average cost of treatment over an extended time period may be less. Economy may also result from a decrease in nursing time and hospitalization time.

➢ **Disadvantages of sustained release drug delivery:**

The disadvantages of sustained release drug delivery system are

- Decreased systemic availability in comparison to immediate release conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time complete release, site specific absorption, pH dependent stability, etc.
- Poor *in vitro – in vivo* correlation.

- Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
- Reduced potential for dose adjustment of drugs normally administered in varying strengths.

iii) Site-specific targeting: Site-specific and receptor targeting refer to targeting of a drug directly to a certain biological location. In the case of site-specific release, the target is adjacent to or in the diseased organ or tissue.

iv) Receptor targeting: For receptor release, the target is the particular receptor for a drug within an organ or tissue. Both of these systems satisfy the spatial aspect of drug delivery and are also considered to be controlled drug-delivery systems.[4]

1.3 EXTENDED RELEASE (ER) TABLETS:

Dosage forms release drug slowly, so that plasma concentrations are maintained at a therapeutic level for a prolonged period of time (usually between 8 and 12 hours).Extended-release medications have special coatings or ingredients that control how fast the drug is released from the pill into your body. This may allow you to take certain medications only once or twice a day, instead of more often.[15]

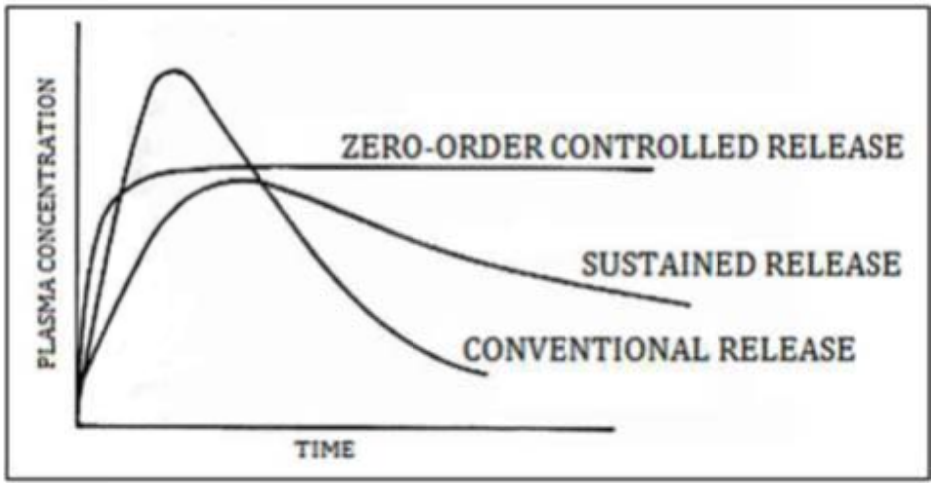


Figure: 1 Controlled release dosage forms

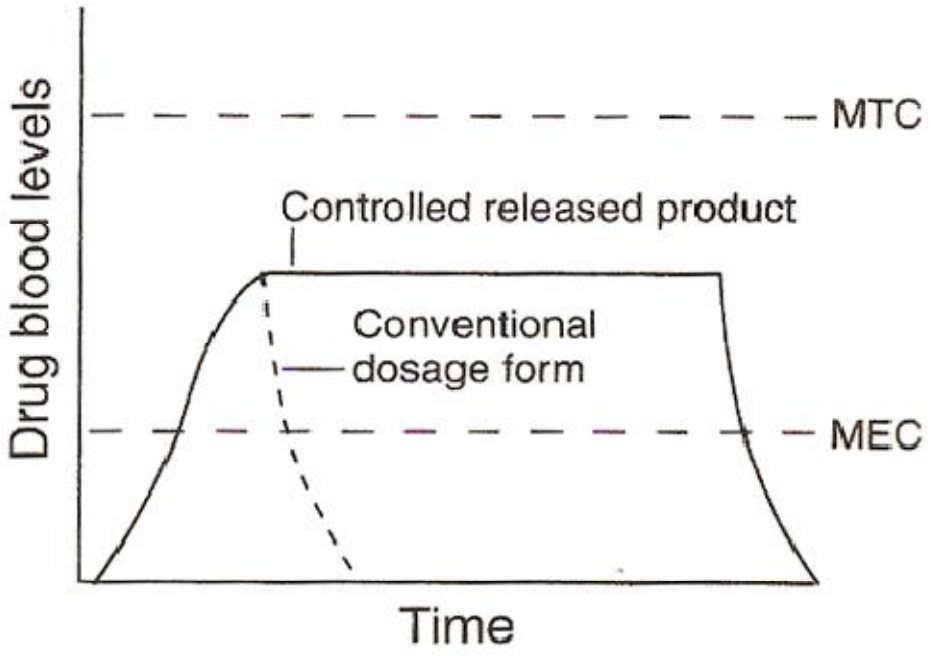


Figure: 2 Controlled release dosage form

1.3.1 ADVANTAGES OF ORAL EXTENDED RELEASE DELIVERY SYSTEM

- Reduce amount of drug administration
- Maximizing availability with minimum dose
- Causes less fluctuation of plasma drug level
- Leads to more uniform drug effect and lesser total dose.
- Improved patient compliance, resulting from the reduction in the number and frequency of doses required to maintain the desired therapeutic response
- There is a reduction in the incidence and severity of localized gastrointestinal side-effects produced by 'dose dumping' of irritant drugs from conventional dosage forms, e.g. potassium chloride. The more controlled, slower release of potassium chloride from it's per oral ER formulations minimizes the build-up of localized irritant concentrations in the gastrointestinal tract. Consequently, potassium chloride is now administered per orally almost exclusively in ER form.

1.3.2 DISADVANTAGES OF ORAL EXTENDED RELEASE DELIVERY SYSTEM

- Generally higher cost,
- Relatively poor in vitro/in vivo correlation,
- Unpredictable and even reduced bioavailability and subjected to increased first pass metabolism for certain drugs. [8]

1.4 TABLET FORMULATION DESIGN:

Tablet formulation design starts with a predetermined value, which is the dose size. The amount of drug in a tablet can be a limiting step in formulation design. Tablet excipients can be classified on the basis of their functionality as listed below:

Fillers/diluents

Binders

Disintegrants

Lubricants

Glidants

Buffering agents

Sweeteners

Wetting agents

Coating agents

Matrix formers

1.4.1 Fillers/diluents used in tablet formulations

- Lactose (a-lactose monohydrate, anhydrite b-lactose, spray-dried lactose)
- Microcrystalline cellulose (Avicel PH 101, Avicel PH 200, Emcocel)

- Starch (Corn starch, partially hydrolyzed starch)
- Dibasic calcium phosphate (Emcompress, Di-Tab)
- Mannitol (Parteck, Delta M)
- Sorbitol (Neosorb 60)
- Calcium sulfate (Delaflo)
- Compressible sucrose (Di-Pac, Des-tab, Nu-Tab)

1.4.2 Binders used in tablet formulations

- Polyvinylpyrrolidone (PVP)
- Sodium carboxymethyl cellulose
- HPMC (Low molecular weight, 5 cps)
- Starch paste
- Simple syrup

1.4.3 Lubricants and glidants used in tablet formulations

- Magnesium stearate
- Stearic acid
- Sodium stearylfumarate
- Hydrogenated vegetable oil
- PEG 4000, 6000
- Hexagonal boron nitride
- DL-Leucine
- Sodium lauryl sulfate

- Glicerylbehenate
- Sodium benzoate
- Colloidal silicone dioxide
- Talc
- Starch

1.4.4 Super disintegrants

- Sodium starch glycolate (Explotab)
- Cross-linked PVP (Polyplasdone XL)
- Cross-linked carboxymethyl cellulose (Ac-Di-Sol)

1.4.5 Coprocessed Excipient Products

Some flexibility is necessary in the design of tablet formulations. Selecting each excipient depends on the physical and chemical properties of the drug, the drug dose, and the required final form and function of the tablet. There are however aids for the formulator. There are some coprocessed excipients containing usually a diluent and binder, and sometimes, even a disintegrant in a readymade granulation. LudipressTM(BASF, Germany) contains a-lactose monohydrate, polyvinylpyrrolidone (PVP), and KollidonCL. Cellactose 80TM (Meggle, Germany) contains a-lactose monohydrate and cellulose powder, ProsolvTM SMCC (JRS Pharma, Germany), silicified MCC, contains 98% MCC and 2% colloidal silicon dioxide, which provides a better granule flow and an opportunity for smaller and denser tablets upon direct compression. There are also coprocessed actives like ascorbic acid, thiamine, riboflavine, pyridoxine, paracetamol and acetyl salicylicacid. For those drugs that are manufactured in huge

volumes, the use of coprocessed excipients is efficient, since the small capacity of many pharmaceutical manufacturing plants for wet or dry granulation cannot deal with huge volumes. Materials that contribute to plastic deformation, which means stronger compacts upon compression or forming a matrix such as methyl cellulose (MC), HPMC, hydoxypropyl cellulose (HPC), cellulose powder, gelatine and mannitol are used. Coprocessed products are so designed that by simple addition of the drug, compressed tablets may be produced. Using coprocessed active allows minimum excipient addition and manipulation.

1.4.6 Fillers/Diluents

Fillers are used to arrive at a tablet of reasonable size when a drug forms a small portion of the formula, as in the case of 25 mg estradiol vaginal tablets. Depending on the physiological conditions and formulation, one needs a tablet of around 100 mg for ease of handling and administration, and therefore, fillers are used to increase bulk. Usually, a-lactose monohydrate is the first material to be considered. This water soluble disaccharide is obtained from whey by crystallization and drying after cheese production. Lactose is a water-soluble diluent, 216 mg dissolving in 1-mL water. Using three different drying techniques, fluidized-bed methods, roller drying, and spray drying, a-lactose monohydrate, anhydrous b-lactose, and spray-dried lactose are obtained, respectively. The three different lactose grades differ considerably in their mechanical properties in relation to tableting. For instance, anhydrous b-lactose shows a steep compression force–tablet crushing strength relation. On the other hand, a-lactose monohydrate and even spray-dried lactose are inferior grades in this respect. Spray drying of lactose forms partial amorphous structures, and that contributes to its better compressibility. Spray-dried lactose flows well because of its spherical granule shape. Therefore, the mechanical properties

and the size distribution of lactose types must be known before making a selection out of many lactose grades. A partial list of excipientsused in tablet manufacturing is following:

1.4.7 Binders

Binders in tablet technology serve the purpose of binding small drug or excipient particles together to impart cohesiveness, and to form a granulate of a designed size range, usually larger than the initial material that flows freely and is also compressible, and eventually to be compressed into tablets or to be filled into capsules. A binder will help the tablet to remain intact after compression. Binders can be added as dry powders to form a matrix that will include the drug, as in the case of dry granulation or in direct compression. Sometimes, the binders are dissolved in liquids such as water or alcohol and then sprayed onto the powder mixture as with wet granulation. Materials such as MCC act as a binder/ diluent in the case of direct compression. However, a polymer such as PVP is solely used as a binder. One of the commercial products of PVP is KollidonTM(BASF), which has grades on the basis of molecular weight of the polymer: Kollidon K 25 (MW 28,000–34,000), K 30 (MW 44,000–54,000), and K 90 (MW 1,000,000–1,500,000) contain PVP of increasing molecular weights. PVP has some advantages over other binders: it is used in relatively small concentrations such as 1% to 5% to prepare a binder solution, itis soluble to above 10% in water, ethanol, and glycerol, which provides an opportunity for water-free granulation. One of the most significant advantages of PVP is its low viscosity (5–10 mPa.sec) even up to concentrations as high as 20% (w/v). A low-viscosity solution can easily be sprayed using peristaltic pumps during a fluidized-bed granulation. Starch paste has been a traditional binder, at concentrations between 5% and 10%. Starch is dispersed in cold water, and then slowly heated up to boiling with constant stirring. When a translucent paste

is formed, it can be diluted with cold water. On the other hand, preparing a starch paste with modified starch will not require boiling, since it dissolves in warm water because of the free amylopectin. In modern granulation processes using highshearmixers, starch paste finds few applications. HPMC, MC, HPC, and ethyl cellulose can be used as binders in tablet formulations. These cellulose-based binders perform as well as PVP in modern granulation processes. Hydrophilic polymers, especially of low molecular weight, for instance HPMC E6 (6 cP viscosity grade), can be dissolved in water to obtain a low-viscosity solution, and they bind well and contribute to plastic deformation during tableting. The high-molecular weight grades of these cellulose based materials can be used as matrix formers, and incorporated into formulations as dry binders. Ethyl cellulose is not water soluble, so it is used as an alcoholic solution. Materials such as PVP and HPMC have largely replaced other binders such as gelatine, sucrose, simple syrup, or acacia.

1.4.8 Disintegrants

Disintegrants serve the purpose of facilitating the disintegration of tablets into itsComponents either after administration in the GI tract or just before administration, suchAs in the case of the fast-disintegrating tablets. Disintegrants may play an important role in the bioavailability of a drug in tablet dose forms. When disintegrantscome into contact with water, they usually swell, as their cross-linked molecular structure, such as in amylose in starch or in cross-linked PVP, imbibes water and swells, providing the force to disperse the tablet. Depending on the formulation design, some tablets containing higher percentages of MCC may disintegrate readily during disintegration tests without an additional disintegrant. Addition of starches externally to the final granulation before tableting is best justified for disintegration

purposes. Starch is a "mild" tablet disintegrant. In the past, there was concern that tablet compression forces should not exceed certain limits or tablet crushing strengths 70 to 80 N because of the probability of prolonged disintegration times. However, with the advent of modern excipients, mechanically strong tablets with 200 to 300 N crushing strengths can be produced, and these tablets will disintegrate within five minutes or less using the super-disintegrants. Super-disintegrants are materials added to tablet formulations in a range of 1% to 5% to assure disintegration within 1 to 10 minutes. Among these are sodium carboxymethyl starch (ExplotabTM, Mendell, U.S.A.), cross-linked sodium carboxymethylcellulose (PharmacelTM XL, DMV, Netherlands), and cross-linked PVP (17) (KollidonTMXL, BASF). The rank order of the degree of swelling in water in two minutes for those disintegrants has been reported to be sodium carboxymethyl starch >sodium carboxymethyl cellulose > L-HPC 11 > cross-linked PVP > starch > MCC.

1.4.9 Lubricants

Pharmaceutical lubricants are materials used in tablet formulations to reduce the friction Between the lower punch and the die and the tablet. Friction damages both the tablet and the tablet press during the ejection cycle. Lubricants are a mechanical necessity, without which modern tablet manufacturing would be impossible. Glidants are materials that reduce interparticular friction, covering the particle surfaces with a thin layer, and as a result helping in better granule flow. Colloidal silicon dioxide, talc, and starch can be used as glidants; colloidal silicon dioxide is effective as low as 0.5% as a glidant. Lubricants are added to pharmaceutical granules just before the tableting stage. Mixing the main granule mass with a lubricant has been an intensively investigated subject. Prolonged mixing with a surface-covering lubricant such as

magnesium stearate negatively affects the binding capacity of a granule mass. Hence, tablet formation might be inhibited, unless the granule mass undergoes brittle fracture and creates new clean surfaces. Especially, materials exhibiting plastic deformation with a limited surface area Would show a strong sensitivity to lubricants. Therefore, the specific surface area of a lubricant as well as the surface area of the granule mass are both important parameters in selecting lubricant type, concentration, and mixing times. Boundary lubricants will adhere on the metal surfaces of the tablet press, die, and punches and will form a boundary layer with the tablet. Alkaline stearates such as magnesium stearate are an example of a boundary lubricant. Magnesium stearate is still the most effective pharmaceutical lubricant. Its usual concentration range is between 0.1% and 2%, and its effectiveness shows a biphasic profile, a region of a fast reduction in friction up to 1 %, and a slower friction-reducing effect after 1%. Magnesium stearate reduces not only the lower punch ejection force by about 70% but also tablet tensile strength. Stearic acid is the second most important lubricant. It is not as effective as magnesium stearate, the minimum effective stearic acid concentration is about 1%, and it reduces the lower punch ejection force no more than 30%. This fatty acid is however useful when an alkaline ingredient in a tablet formula is undesirable. The hexagonal form of boron nitride (HBN) has been reported as a potential tablet lubricant. HBN is similar to graphite, which is soft and lubricious. This inorganic solid powder retains its ability to lubricate in extreme cold or heat.It was reported that boron nitride reduced the lower punch ejection force as efficiently as magnesium stearate, but its ability to reduce the tablet tensile strength is less than magnesium stearate. The result is mechanically stronger tablets. Therefore, there is a good potential for HBN to be used as a tablet lubricant. For effervescent tablets, water-soluble lubricants are required since insoluble alkaline lubricants would accumulate on the surface of final solution or form a

cloudy solution with an alkaline taste, all of which is undesirable. Sodium lauryl sulfate, DL-leucine, or various PEGs can be used as water-soluble lubricants. Liquid paraffin and hydrogenated vegetable oil are also among the lubricants, but their effectiveness is lower than that of magnesium stearate and stearic acid.[3]

1.5 TABLET-MANUFACTURING OPERATIONS:

There are three general methods of tablet preparation.

- Direct compression method
- Dry granulation method
- Wet granulation method

1.5.1 Direct compression

Direct compression is the process by which tablets are compressed directly from powder mixture of API and suitable excipients. This method of tablet making is of special interest for small group of crystalline chemicals having the entire physical characteristic necessary for the formulation of a good tablet.

- **Advantages**

1. The most important advantage of direct compression is economical process. Reduced processing times, reduced labors costs, fewer manufacturing steps and less number of equipment's are required, less process validation, reduced consumption of power.
2. Elimination of heat and moisture, thus increasing not only the stability but also the suitability of the process for themolabile and moisture sensitive API's.
3. Particle size uniformity.
4. The chances of batch-to-batch variation are negligible, because the unit operations required for manufacturing processes is fewer.

5. Chemical stability problems for API and excipients would be avoided.
6. Provides stability against the effect of aging which affects the dissolution rates.

- **Disadvantages**

1. Problems in the uniform distribution of low dose drugs.
2. The choice of excipients for direct compression is extremely critical. Direct compression diluents and binders must possess both good compressibility and good flowability.
3. Many active ingredients are not compressible either in crystalline or amorphous forms.
4. Direct compression blends may lead to unblending because of difference in particle size and density of drug and excipients. Similarly the lack of moisture may give rise to static charges, which may lead to unblending.
5. Non-uniform distribution of colour, especially in tablets of deep colours.

1.5.2 Dry granulation method

This process of granulation is also known as slugging, double compression or recompression method. This process of tablet preparation is commonly used when the tablet ingredients are sensitive to moisture or are unable to withstand elevated temperature during drying. Under such conditions dry granulation is the method of choice provided the tablet ingredients have sufficient inherent binding or cohesive properties.

- **Advantages**

1. It uses less equipment's and space.
2. It eliminates the need for binder solution, heavy mixing equipment and the costly and time consuming drying step required for wet granulaion.
3. It can be used for moisture sensitive and heat sensitive materials.
4. For improved disintegration since powder particles are not bonded together by a binder.

- **Disadvantages**

1. It requires a specialized heavy duty tablet press to form slug.
2. It does not permit uniform colour distribution as can be achieved with wet granulation where the dye can be incorporated into binder liquid.
3. The process tends to create more dust than wet granulation, increasing the potential contamination.

1.5.3 Wet granulation method

Wet granulation process simply involves wet massing of the powder blend with a granulating liquid, wet sizing and drying.

- **Advantage**

1. It is a robust process suitable for most compounds.
2. It imparts flowability to a formulation.
3. It can reduce elasticity problems.
4. In this process drug binds with excipients, thus reduces segregation potential.
5. Non aqueous wet granulation process is suitable for moisture sensitive drugs.

- **Disadvantages**

1. The greatest disadvantage of wet granulation is its cost. It is an expensive process because of labour, time, equipment, energy and space requirements.
2. Loss of material during various stages of processing.
3. Stability may be major concern for moisture sensitive or thermo labile drugs.
4. Multiple processing steps add complexity and make validation and quality control difficult.
5. An inherent limitation of wet granulation is that any incompatibility between formulation components is aggravated.[6]

1.6 MECHANISM OF GRANULE FORMATION:

Granules are formed in three stages:

1.6.1 Nucleation;

Here, the particles adhere due to liquid bridges which are the initiation step of Granulation. These adhered particles play a role of nucleus for further enlargement of granules.

1.6.2 Transition;

Enlargement of nucleus takes place by two possible mechanisms. Individual particle adhere to the nucleus or two or more nuclei combine among themselves.

1.6.3 Ball growth or enlargement of the granule;

Ball growth occurs either by Coalescence or Breakage or Abrasion Transfer or Layering. In Coalescence a larger granule is formed when two or more granules are united. In Breakage granules break and the fragments of granule adhere to other granules. This forms a layer of material over intact granules. In Abrasion Transfer granule material are abraded through attrition by the agitation of granule bed and abraded material adheres to other granules resulting into enlarged granules. In layering particles adheres to the already formed granules increasing their size.

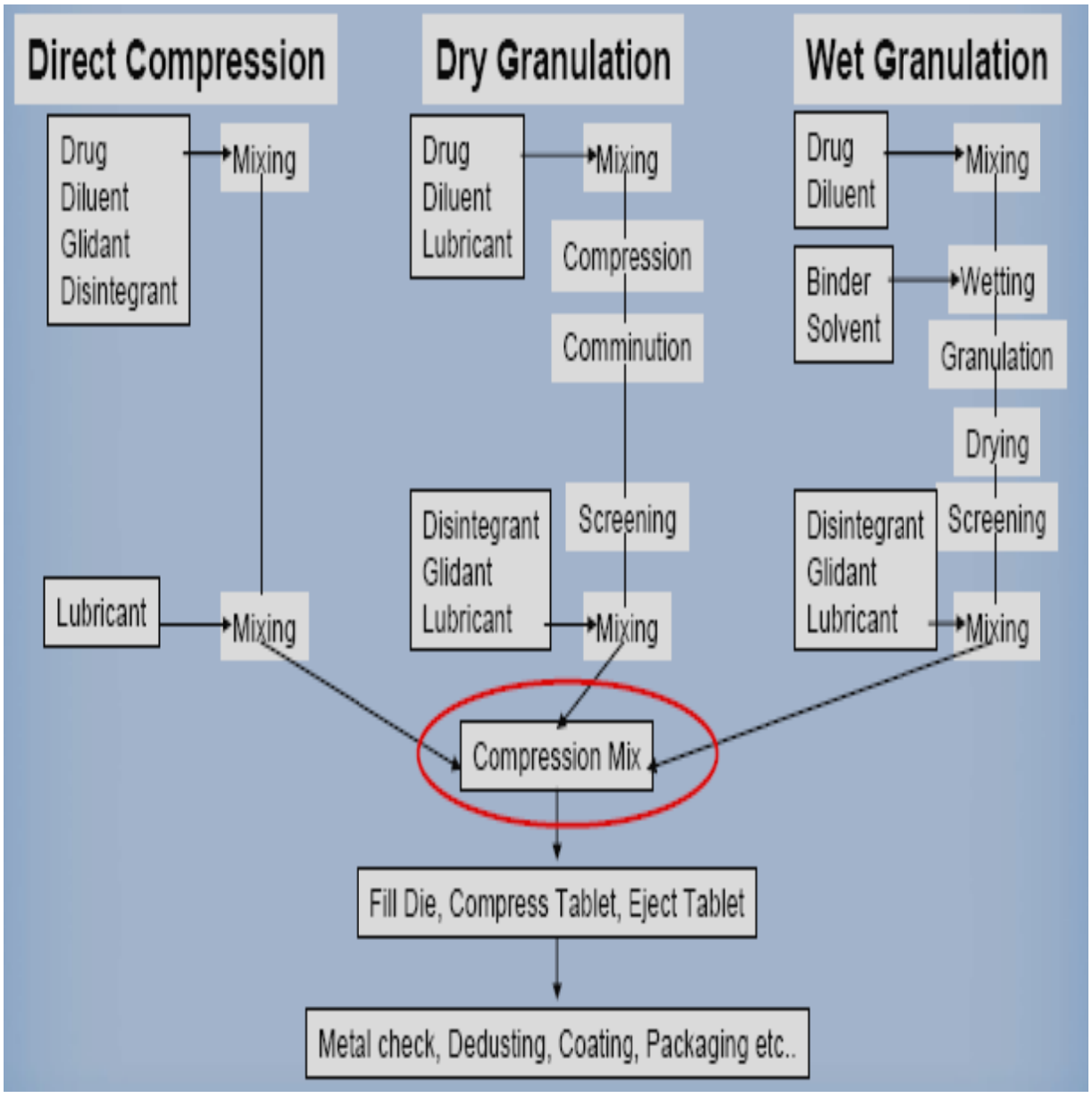


Figure: 3 Unit operations involved in wet granulation, dry granulation and direct compression

1.7 COMPRESSION

After the preparation of lubricated granules they are compressed to get the final product. The compression is done either by single punch machine (Stamping press) or by multi station machine (Rotary press). The punches and dies are fixed to a turret that spins round. As it spins, the punches are driven together by two fixed cams – an upper cam and a lower cam. The punch head (top of the upper punch) sits on the upper cam edge. The bottom of the lower punch sits on the lower cam edge. The shapes of the two cams determine the sequence of movements of the two punches. This sequence is repeated over and over because the turret is spinning round. The force exerted on the ingredients in the dies is very carefully controlled. This ensures that each tablet is perfectly formed. [6]

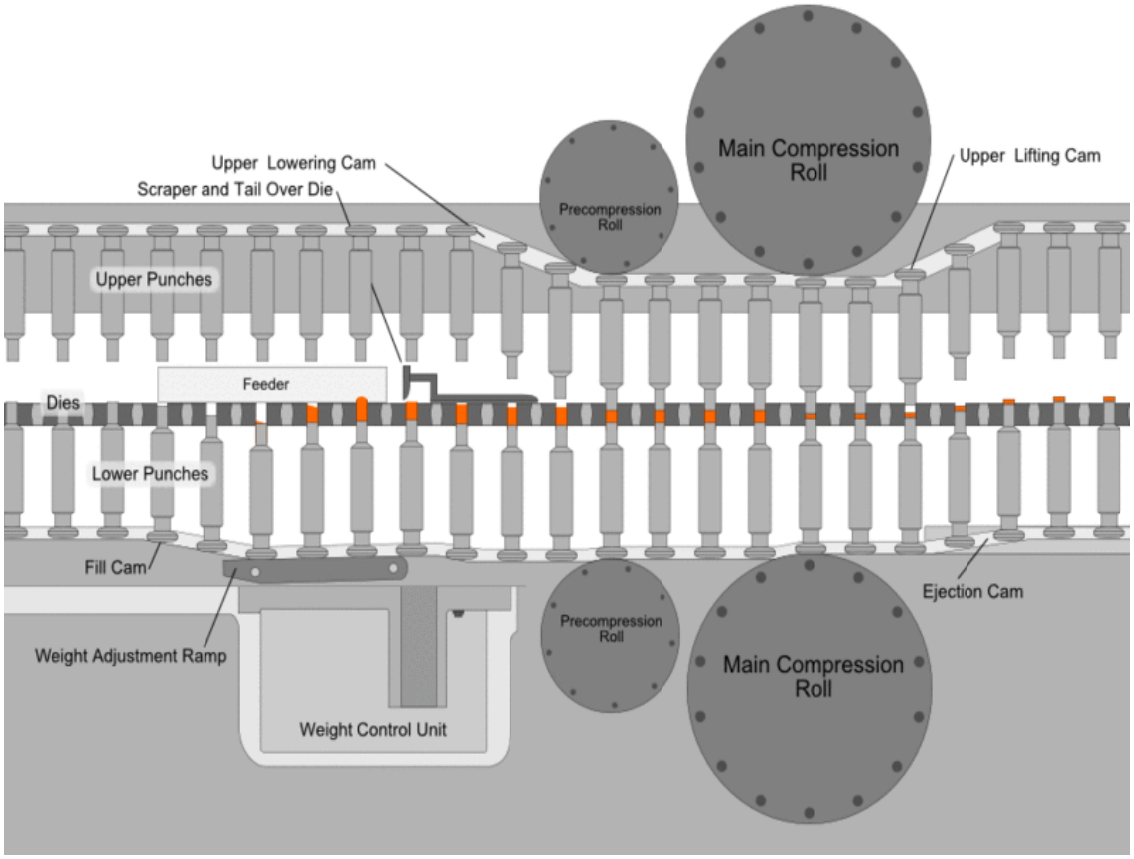


Figure: 4 Tablet compression machine

1.8 TABLET COATING:

Coating is a process by which an essentially dry, outer layer of coating material is applied to the surface of a dosage form in order to confer specific benefits that broadly ranges from facilitating product identification to modifying drug release from the dosage form. After making a good tablet, one must often coat it. Coating may be applied to a wide range of oral solid dosage form, including tablets, capsules, multiparticulates and drug crystals. When coating composition is applied to a batch of tablets in a coating pan, the tablet surfaces become covered with a tacky polymeric film. Before the tablet surface dries, the applied coating changes from a sticky liquid to tacky semisolid, and eventually to a non sticky dry Surface pans. The entire coating process is conducted in a series of mechanically operated acorn-shaped coating pans of galvanized iron stainless steel or copper. The smaller pans are used for experimental, developmental, and pilot plant operations, the larger pans for industrial production

1.8.1 Basic principles involve in tablet coating

Tablet coating is the application of coating composition to moving bed of tablets with concurrent use of heated air to facilitate evaporation of solvent.

a. Solution in which influences the release pattern as little as possible and does not markedly change the appearance.

b. Modified release with specific requirement and release mechanism adapted to body function in the digestive tract.

c. Color coating which provides insulation.

d. To incorporate another drug or formula adjuvant in the coating to avoid chemical incompatibilities or to provide sequential drug release.

e. To improve the pharmaceutical elegance by use of special colors and contrasting printing.

1.8.2 Film-coated tablets

A film-coated tablet is covered with a thin layer of resins, polymers and/or plasticizers capable of forming a film.

1.8.2.1 Disintegration test

Film-coated tablets comply with 5.3 Disintegration test for tablets and capsules. Operate the apparatus for 30 minutes, and examine the state of the tablets.[12]

1.9 QUALITY CONTROL OF TABLETS:

After manufacturing tablets, a series of tests are carried out to assure that they meet the Specifications of pharmacopoeia or industry standards. These tests are as listed below:

- Crushing strength
- Disintegration
- Friability
- Dissolution
- Drug content uniformity
- Weight uniformity
- Weight and thickness

Some tablets are ready to be used after manufacture, while some need to be coated For further functional properties such as enteric coating or controlled-release coating.[7]

2 LITERATURE REVIEW

2.1 Lloyd N et al; The use of extended-release products offers some potential advantages in patient convenience/compliance and therapeutic outcomes. However, the range of drugs for which clinically significant advantages have been shown is limited. Prescribers and pharmacists should be aware of the costs of these products and have a knowledge of their clinical use in selected patient groups. In some instances, the formulation is probably serving a marketing objective rather than a clinical objective.

2.2Navin Dixit et al; The oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes. The terms Sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. There are several reasons for attractiveness of these dosage forms: provides increased bioavailability of drug product, reduction in the frequency of administration to prolong duration of effective blood levels, reduces the fluctuation of peak trough concentration and side effects and possibly improves the specific distribution of the drug.

2.3 K.P. Sampath Kumar et al;Pharmaceutical invention and research are increasingly focusing on delivery systems which enhance desirabletherapeutic objectives while minimizing side effects. Oral drug delivery system represents one of the frontier areasof controlled drug delivery system. Such a dosage forms having a major advantage of patient compliance. Sustainedrelease dosage forms are designed to release a drug at a predetermined rate in order to maintain a

constant drug concentration for a specific period of time with minimum side effects. Now a days as very few drugs are coming out of research and development and already existing drugs are suffering the problem of resistance due to their irrational use specifically in case of drugs like antibiotics. Hence, change in the operation is a suitable and optimized way to make the some drug more effective by slight alteration in the drug delivery. Sustained Release is also providing promising way to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body.

2.4 Christenson et al; This invention provides extended release potassium chloride granules consisting essentially of potassium chloride crystals having a mesh size of about 20—60 mesh that are coated only With ethyl cellulose. The granules may be compressed into tablets that disintegrate rapidly in an aqueous environment to provide uniform dissolution of the potassium chloride. Tablets containing about 10 to about 20 milliequivalents potassium may be formulated in accordance With the invention. Processes to produce extended release granules without using surfactants, processing aids or other coating aids are also provided by this invention. A method is further provided whereby a patient's supplemental potassium requirements are met by administering an appropriate combination of dosage units chosen from available dosage units containing different quantities of potassium.

2.5Alsop WR, et al; the effects on the upper gastrointestinal tract of five different preparations of KCl were compared in 90 healthy subjects treated with glycopyrrolate. The KCl preparations studied were wax-matrix KCl, microencapsulated KCl, liquid KCl, experimental extended-release capsules, experimental extended-release tablets, and placebo. The subjects were endoscoped prior to and after seven days of dosing. Upper gastrointestinal mucosal pathology

was seen with all of the potassium preparations as well as with placebo. No statistically significant differences between the various KCl groups or between KCl groups and placebo were seen. All of the lesions were superficial, except for one ulcer seen with the microencapsulated KCl. None of the subjects developed occult gastrointestinal bleeding. There were no differences in the incidence of abdominal symptoms.

2.6 Dr. D. M. Patel et al; the objective of the present study was to evaluate the effect of sintering condition on matrix formation and subsequent drug release from polymer matrix tablet for controlled release. The present study highlights the use of a microwave oven for the sintering process in order to achieve more uniform heat distribution with reduction in time required for sintering. We could achieve effective sintering within 8 min which is very less compared to conventional hot air oven sintering. The tablets containing the drug (propranolol hydrochloride) and sintering polymer, were prepared and kept in a microwave oven at 540 watt, 720 watt and 900 watt power for different time periods for sintering. The sintered tablets were evaluated for various tablet characteristics including dissolution study. Tablets sintered at 900 watt power for 8 min gave better dissolution profile compared to others. We conclude that microwave oven sintering is better than conventional hot air oven sintering process in preparation of controlled release tablets.

2.7 Monica Rao et al; The present research studied the effect of sintering technique in the development of a controlled release formulation for ketorolac tromethamine. The method consisted of mixing drug and wax powder (Compritol® 888 ATO) along with lactose as diluent and talc as lubricant followed by direct compression at room temperature. The compressed fluffy matrices were kept at 80°C for 1, 2, and 3 h forsintering. The sintered tablets were characterized

by their physical parameters and in vitro dissolution profile. The sintering time markedly affected the drug release properties of Compritol® 888 ATO matrices. It is notable that the release rate of ketorolac tromethamine from matrices was inversely related to the time of sintering. This may be due to the increase in the extent and firmness of sintering which further compacts the mass so that drug release is affected. Contact angle measurement and scanning electron microscopy analysis indicated that heat treatment caused the wax to melt and redistribute. This redistributed wax formed a network-like structure in which the drug along with lactose is entrapped. This particular formed matrix is responsible for retarding the drug release. Fourier transform infrared spectroscopy results did not show any drug–wax interaction due to sintering. Differential scanning calorimetric and powder X-ray diffraction studies ruled out the occurrence of solid solution and polymorphic changes of the drug. Drug release from the wax tablets with or without sintering was best described by the Higuchi equation.

2.8 Sunil Kumar et al; Oral drug delivery is the most preferred route for the various drug molecules among all other routes of drug delivery, because ease of administration which lead to better patient compliance. So, oral extended release drug delivery system becomes a very promising approach for those drugs that are given orally but having the shorter half-life and high dosing frequency. Extended release drug delivery system which reduce the dosing frequency of certain drugs by releasing thedrug slowly over an extended period of time. There are various physiochemical and biological properties which affect the extended release drug delivery system. This article providing the recent literature regarding development and design of extended release tablets.

2.9 K. P. R. Chowdary et al; Formulation and manufacture of matrix tablets is a least complicated approach widely used in industry for obtainingoral controlled release. Matrix tablet formulation needs an efficient release retarding material, which plays a critical role in regulating drug release from matrix tablets. Literature on matrix tablets along with recent research on matrix tablets for controlled release is reviewed in this article.

3.AIM & OBJECTIVES

Patients who cannot tolerate or refuse to take liquid or effervescent potassium preparations or for patients in whom there is a problem of compliance with these preparations.

The aims of the present study were to formulate and evaluate potassium chloride extended release tablets

The study was carried out in the following stages:

- To Development and in vitro evaluation of potassium chloride extended release tablets
- To carry out pre-formulation studies
- To carry out the stability studies of the formulated extended release dosage form as per ICH guidelines

4. PLAN OF WORK

This research work comprises the following

1. Literature review
2. Selection of excipients from the reference literature
3. Selection of excipients quantity from available reference product.
4. Preformulation studies.
5. Formulation of Trial Batches.
6. Evaluation of Pre-compression and Post-compression characteristics.
7. Selection of final formulation.
8. Comparison of dissolution profile between finalized potassium chloride formulation and reference product.
9. Stability studies for the finalized potassium chloride formulation.
10. Comparison of drug release with the reference product.

5. MATERIELS AND METHODS

5.1 List of materials and their manufacturers or suppliers.

Table No: 1

S.No	Materials	Functions	Manufacturers/suppliers
1.	Potassium chloride	Active Ingredient	Klinge Chemicals Limited
2.	Hydrogenated vegetable oil	Release controlling agent	Abitech corporation
3.	Ethocel 100 FP	Release controlling agent	Colorcon asiapvt lid
4.	Ethocel 10 FP	Binder	Colorcon asiapvt lid
5.	Colloidal silicon dioxide	Glidant	Cabot Sanmar lid
6.	Talc	Glidant& Lubricant	Luzenac
7.	Syloid	Glidant	Grace Davison
8.	Magnesium stearate	Lubricant	Valerus speciality chemicals
9.	Iso propyl alcohol	Solvent	Merck
10.	OpadryII85F520112 Yellow	Coating material	Colorcon asia pvt lid

5.2 LIST OF EQUIPMENTS USED

The following equipment's and instruments were used in the formulation and development of potassium chloride Extended release tablets.

Table no: 2

S. No.	NAME OF THE INSTRUMENT	MAKE
1.	Analytical balance	Sartorius
2.	Electromagnetic Sieve Shaker	Electro Lab
3.	Tap Density Apparatus	Electro Lab
4.	Moisture Analyzer	Sartorius
5.	Tablet Compression Machine	Cad Mach
6.	Tablet Coating Machine	Siemens
7.	Digital Vernier Caliper	Mitutoyo
8.	Disintegration tester	Electro Lab
9.	Friability apparatus	Electro Lab
10.	Dissolution	Electro Lab
11.	HPLC	Thermo scientific
12.	Stability Chamber	Thermo lab
13.	Fluid bed equipment	Pam Glatt
14.	Rapid mixing Granulation	Anchor mark
15.	Octagonal blender	Anchor mark
16.	Multi Mill	Anchor mark

5.3 EXCIPIENT SELECTION:

Excipients used in the present work were selected according to innovator excipient list.

Excipients includes

- Hydrogenated vegetable oil
- Ethocel 100 fp
- Ethocel 10 fp
- Colloidal silicon dioxide
- Talc
- Magnesium stearate

5.3.1 HYDROGENATED VEGETABLE OIL

a) Chemical Name and CAS Registry Number

- Hydrogenated vegetable oil
- Hydrogenated soybean oil

b) Structural Formula

R1COOCH2—CH(OOCR2)—CH2OOCR3

where R1, R2, and R3 are mainly C15 and C17.

c) Description:

Hydrogenated vegetable oil is a mixture of triglycerides of fattyacids. The two types that are defined in the USP32–NF27 arecharacterized by their physical properties. Hydrogenated vegetable oil type I occurs in various forms, e.g.fine powder, flakes, or pellets. The color of the material depends onthe manufacturing process and the form. In general, the material iswhite to yellowish-white with the powder grades appearing morewhite-colored than the coarser grades.

d) Functional Category

Tablet and capsule lubricant; tablet binder.

e) Applications in Pharmaceutical Formulation orTechnology

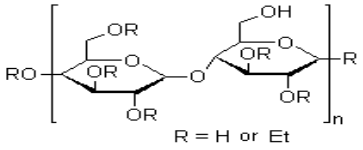
Hydrogenated vegetable oil type I may be used as a lubricant in tablet and capsule formulations. In this application it is used at concentrations of 1–6% w/w, usually in combination with talc, silica or a silicate to prevent sticking to tablet punch faces. It may also be used as an auxiliary binder in tablet formulations. Hydrogenated vegetable oil type I is additionally used as the matrix-forming material in lipophilic-based controlled-release formulations; it may also be used as a coating aid in controlled-release formulations. It has also been investigated in hydrophobic melt agglomeration.

5.3.2 ETHYL CELLULOSE

a) Chemical Name and CAS Registry Number

Cellulose ethyl ether

b) Molecular structure



c) Description

Ethylcellulose is a tasteless, free-flowing, white to light tan-colored powder.

d) Functional Category

Coating agent; flavoring agent; tablet binder; tablet filler; viscosity increasing agent.

e) Method of Manufacture

Ethylcellulose is prepared by treating purified cellulose (sourced from chemical-grade cotton linters and wood pulp) with an alkaline solution, followed by ethylation of the alkali cellulose with chloroethane as shown below, where R represents the cellulose radical:

$$RONa + C_2H_5Cl \rightarrow ROC_2H_5 + NaCl$$

The manner in which the ethyl group is added to cellulose can be described by the degree of substitution (DS). The DS designates the average number of hydroxyl positions on the

anhydroglucose unit that have been reacted with ethyl chloride. Since each anhydroglucoseunit of the cellulose molecule has three hydroxyl groups, the maximum value for DS is three.

f) Incompatibilities

Incompatible with paraffin wax and microcrystalline wax.

g) Applications in Pharmaceutical Formulation or Technology

Ethylcellulose is widely used in oral and topical pharmaceutical formulations, the main use of ethylcellulose in oral formulations is as ahydrophobic coating agent for tablets and granules. Ethylcellulose coatings are used to modify the release of a drug, to mask an unpleasant taste, or to improve the stability of a formulation; for example, where granules are coated with ethylcellulose to inhibit oxidation. Modified-release tablet formulations may also be produced using ethylcellulose as a matrix former. Ethylcellulose, dissolved in an organic solvent or solvent mixture, can be used on its own to produce water-insoluble films. Higher-viscosity ethylcellulose grades tend to produce stronger and more durable films. Ethylcellulose films may be modified to alter their solubility, by the addition of hypromellose or aplasticizer; Drug release through ethylcellulose-coated dosage forms can be controlled by diffusion through the film coating. This can be a slow process unless a large surface area (e.g. pellets or granules compared with tablets) is utilized. In those instances, aqueous ethylcellulose dispersions are generally used to coat granules or pellets. Ethylcellulose-coated beads and granules have also demonstrated the ability to absorb pressure and hence protect the coating from fracture during compression.

5.3.3 COLLOIDAL SILICON DIOXIDE

a) Chemical Name and CAS Registry Number

Silica

b) Description

Colloidal silicon dioxide is a submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, amorphous powder.

c) Functional Category

Adsorbent; anticaking agent; emulsion stabilizer; glidant; suspending agent; tablet disintegrant; thermal stabilizer; viscosity-increasing agent.

d) Incompatibilities

Incompatible with diethylstilbestrol preparations.

e) Method of Manufacture

Colloidal silicon dioxide is prepared by the flame hydrolysis of chlorosilanes, such as silicon tetrachloride, at 1800◦C using a hydrogen–oxygen flame. Rapid cooling from the molten stateduring manufacture causes the product to remain amorphous.

f) Applications in Pharmaceutical Formulation or Technology

Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products. Its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powdersin a number of processes such as tableting and capsule filling. Colloidal silicon dioxide is also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid

preparations. With other ingredients of similar refractive index, transparent gels may be formed. The degree of viscosity increase depends on the polarity of the liquid (polar liquids generally require a greater concentration of colloidal silicon dioxide than nonpolar liquids). Viscosity is largely independent of temperature. However, changes to the pH of a system may affect the viscosity. In aerosols, other than those for inhalation, colloidal silicon dioxide is used to promote particulate suspension, eliminate hard settling, and minimize the clogging of spray nozzles. Colloidal silicon dioxide is also used as a tablet disintegrant and as an adsorbent dispersing agent for liquids in powders. Colloidal silicon dioxide is frequently added to suppository formulations containing lipophilic excipients to increase viscosity, prevent sedimentation during molding, and decrease the release rate. Colloidal silicon dioxide is also used as an adsorbent during the preparation of wax microspheres; as a thickening agent for topical preparations and has been used to aid the freeze-drying of nanocapsules and nanosphere suspensions.

5.3.4 TALC

a) Chemical Name and CAS Registry Number

Talc

b) Functional Category

Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

c) Description

Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

d) Incompatibilities

Incompatible with quaternary ammonium compounds.

e) Method of Manufacture

Talc is a naturally occurring hydropolysilicate mineral found in many parts of the world including Australia, China, Italy, India, France, and the USA. The purity of talc varies depending on the country of origin. For example, Italian types are reported to contain calcium silicate as the contaminant; Indian types contain aluminum and iron oxides; French types contain aluminum oxide; and American types contain calcium carbonate (California), iron oxide (Montana), aluminium and iron oxides (North Carolina), or aluminum oxide (Alabama).Naturally occurring talc is mined and pulverized before being subjected to flotation processes to remove various impurities such as asbestos (tremolite); carbon; dolomite; iron oxide; and various other magnesium and carbonate minerals. Following this process, the talc is finely powdered, treated with dilute hydrochloric acid, washed with water, and then dried. The processing variables of agglomerated talc strongly influence its physical characteristics.

f) Applications in Pharmaceutical Formulation or Technology

Talc was once widely used in oral solid dosage formulations as a lubricant and diluent, although today it is less commonly used. However, it is widely used as a dissolution retardant in the development of controlled-release products. Talc is also used as a lubricant in tablet formulations; in a novel powder coating for extended-release pellets; and as an adsorbant. In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves. Talc is a natural material; it may therefore frequently contain microorganisms and should be sterilized when used as a dusting powder, Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

5.3.5 MAGNESIUM STEARATE

a) Chemical Name and CAS Registry Number

Octadecanoic acid magnesium salt

b) Structural Formula

[CH3 (CH2)16COO] 2Mg

c)Functional Category

Tablet and capsule lubricant.

d)Incompatibilities

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be usedin products containing aspirin, some vitamins, and most alkaloidal salts.

e) Method of Manufacture

Magnesium stearate is prepared either by the interaction of aqueous solutions of magnesium chloride with sodium stearate or by the interaction of magnesium oxide, hydroxide, or carbonate with stearic acid at elevated temperatures.

f) Description

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

g) Applications in Pharmaceutical Formulation or Technology

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25%and 5.0% w/w. It is also used in barrier creams.[3]

6. DRUG PROFILE

Table No: 3 Details of Drugs

Category	Electrolyte replenisher.
Description	white crystalline solid
Chemical Name	Potassium chloride
Chemical Formula	Cl K
Chemical Structure	
Molecular Weight	74.5513 $g \cdot mol^{-1}$
Melting Point	770 °C (1,420 °F; 1,040 K)
Boilng Point	1,420 °C (2,590 °F; 1,690 K)
Refractive Index	1.4902 (589 nm)
Solubility	soluble in glycerol, alkalies slightly soluble in alcohol, insoluble in ether[1]
Storage	Store in a cool, dry place. Temperature range 5-30°C.

6.1 INDICATIONS AND USAGE

Because of reports of intestinal and gastric ulceration and bleeding with controlled-release potassium chloride preparations, these drugs should be reserved for those patients who cannot tolerate or refuse to take liquid or effervescent potassium preparations or for patients in whom there is a problem of compliance with these preparations.

- For the treatment of patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication, and in patients with hypokalemic familial periodic paralysis. If hypokalemia is the result of diuretic therapy, consideration should be given to the use of a lower dose of diuretic, which may be sufficient without leading to hypokalemia.
- For the prevention of hypokalemia in patients who would be at particular risk if hypokalemia were to develop, eg, digitalized patients or patients with significant cardiac arrhythmias.

The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern and when low doses of the diuretic are used. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases, and if dose adjustment of the diuretic is ineffective or unwarranted, supplementation with potassium salts may be indicated.[17]

6.2 DOSAGE ADMINISTRATION:

The usual dietary potassium intake by the average adult is 50 to 100 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires the loss of 200 or more mEq of potassium from the total body store. Dosage must be adjusted to the individual needs of each patient. The dose for the prevention of hypokalemia is typically in the range of 20 mEq per day. Doses of 40-100 mEq per day or more are used for the treatment of potassium depletion. Dosage should be divided if more than 20 mEq per day is given such that no more than 20 mEq is given in a single dose. Potassium Chloride extended-release tablets provide 8 mEq, 10 mEq and 20 mEq of Potassium Chloride.

Potassium Chloride extended-release tablets should be taken with meals and with a glass of water or other liquid. This product should not be taken on an empty stomach because of its potential for gastric irritation (see WARNINGS).

(NOTE: Potassium Chloride extended-release tablets are to be swallowed whole without crushing, chewing or sucking the tablets.)

6.3 CLINICAL PHARMACOLOGY:

6.3.1 MECHANISM OF ACTION:

Supplemental potassium in the form of high potassium food or potassium chloride may be able to restore

6.3.2 ABSORPTION AND DISTRIBUTION:

Potassium is a normal dietary constituent and under steady-state conditions the amount of potassium absorbed from the gastrointestinal tract is equal to the amount excreted in the urine.

6.3.3 METABOLISM AND EXCRETION:

Supplemental potassium in the form of high potassium food or potassium chloride may be able to restore normal potassium.[18]

6.4 PHARMACODYNAMICS:

The potassium ion is in the principle intracellular cation of most body tissues. Potassium ions participate in a number of essential physiological processes including the maintenance of intracellular tonicity, the transmission of nerve impulses, the contraction of cardiac, skeletal and smooth muscle, and the maintenance of normal renal function. The intracellular concentration of potassium is approximately 150 to 160 mEq per liter. The normal adult plasma concentration is 3.5 to 5 mEq per liter. An active ion transport system maintains this gradient across the plasma membrane. Potassium is a normal dietary constituent and under steady-state conditions the amount of potassium absorbed from the gastrointestinal tract is equal to the amount excreted in the urine. The usual dietary intake of potassium is 50 to 100 mEq per day. Potassium depletion will occur whenever the rate of potassium loss through renal excretion and/or loss from the gastrointestinal tract exceeds the rate of potassium intake. Such depletion usually develops as a consequence of therapy with diuretics, primarily or secondary hyperaldosteronism, diabetic ketoacidosis, or inadequate replacement of potassium in patients on prolonged parenteral nutrition. Depletion can develop rapidly with severe diarrhea, especially if associated with vomiting. Potassium depletion due to these causes is usually accompanied by concomitant loss of chloride and is manifested by hypokalemia and metabolic alkalosis. Potassium depletion may produce weakness, fatigue, disturbances of cardiac rhythm (primarily ectopic beats), prominent U-waves in the electrocardiogram, and, in advanced cases, flaccid paralysis and/or impaired

ability to concentrate urine. If potassium depletion associated with metabolic alkalosis cannot be managed by correcting the fundamental cause of the deficiency, e.g., where the patient requires long-term diuretic therapy, supplemental potassium in the form of high potassium food or potassium chloride may be able to restore normal potassium levels. In rare circumstances (e.g., patients with renal tubular acidosis) potassium depletion may be associated with metabolic acidosis and hyperchloremia. In such patients, potassium replacement should be accomplished with potassium salts other than the chloride, such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.[38]

6.5 WARNINGS:

- Upset stomach, nausea, vomiting, gas, or diarrhea may occur. If any of these effects persist or worsen, tell your doctor or pharmacist promptly.
- An empty tablet or capsule shell may appear in your stool. This effect is harmless because your body has already absorbed the medication.
- Remember that your doctor has prescribed this medication because he or she has judged that the benefit to you is greater than the risk of side effects. Many people using this medication do not have serious side effects.
- Tell your doctor right away if you have any serious side effects, including: difficult/painful swallowing, feeling as if the capsule/tablet is stuck in your throat.
- Get medical help right away if you have any very serious side effects, including: vomit that looks like coffee grounds, stomach/abdominal pain, black/tarry stools.

- A very serious allergic reaction to this drug is rare. However, get medical help right away if you notice any symptoms of a serious allergic reaction, including: rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing.

6.6 PRECAUTIONS:

- Before taking potassium, tell your doctor or pharmacist if you have any allergies. This product may contain inactive ingredients, which can cause allergic reactions or other problems. Talk to your pharmacist for more details.
- Before using this medication, tell your doctor or pharmacist your medical history, especially of: heart problems, kidney problems, high levels of potassium in the blood.
- Due to rare reports of stomach/intestinal ulcers and bleeding with sustained-release potassium products, taking a liquid form of potassium is preferred. Tell your doctor or pharmacist if you have throat/stomach/intestinal problems such as blockage, narrowing, or ulcers.
- Before having surgery, tell your doctor or dentist about all the products you use (including prescription drugs, nonprescription drugs, and herbal products).
- Before using other potassium supplements or salt substitutes that contain potassium, consult your doctor or pharmacist. Too much potassium may cause serious side effects. (See also Overdose section.)
- During pregnancy, this medication should be used only when clearly needed. Discuss the risks and benefits with your doctor.

- Potassium passes into breast milk. Consult your doctor before breast-feeding.

- Orally, potassium chloride is toxic in excess; the LD50 is around 2.5 g/kg (meaning that a lethal dose for 50% of people weighing 75 kg (165 lb) is about 190 g (6.7 ounces)). However, this is not far from oral toxicity of sodium chloride (table salt), of 3.75 g/kg, thus potassium chloride is harmless for alimentation (and even good for health, see previous paragraph). But intravenously, without the step of digestive absorption, this is reduced to just over 30 mg/kg.[15] Most concerns are its severe effects on the cardiac muscles: high doses can cause cardiac arrest and rapid death, thus the aforementioned use as the third and final drug delivered in the lethal injection process.[46]

6.7 ACTIVE PHARMACEUTICAL INGREDIENT (API) SPECIFICATION

Table: 4 API Characterization

S.NO.	TESTS	VALUES
1	Appearance	white crystalline solid
2	Solubility in water	281 g/L (0 °C) 344 g/L (20 °C) 567 g/L (100 °C)
3	Heavy metals	<10ppm
4	Water content (by KF)	74.9
5	Assay (on anhydrous basis, by HPLC)	99.66%

6.8 REFERENCE PRODUCT COMPOSITION & CHARACTERIZATION:

Figure: 5 Picture of reference kcl ER tablets

Table No: 5 Reference Products details

Product	Klor-Con 10 mEq
Label claim	Each tablet contains Potassium Chloride 750 mg
NDC	0245-0041-11
Lot.No	310261
ExpDt	06-18
Manufactured By	Upsher -Smith laboratories inc
Storage	Store at controlled room temperature, 15-30°C (59-86°F). Protect from light and moisture. Dispense in a tight container with child-resistant closure.
Excipients	Hydrogenated vegetable oil, magnesium stearate, polyethylene glycol, polyvinyl alcohol, silicon dioxide, talc and titanium dioxide. Yellow tablets also contain D&C Yellow No. 10 aluminum lake and FD&C Yellow No. 6 aluminum lake.
Coated Tablet	
Description	Yellow round tablets debossed with 'KC 10'
Avgwt	1016 mg (996-1030 mg)
Diameter	13 mm
Thickness	6.35-6.40 mm
Hardness	90-110N
D.T	Up to three hours disintegration is not observed
Core Tablet	
Avgwt	980 mg
Diameter	12.7 mm
Thickness	6.35-6.40 mm
Hardness	80-90N
Pack	100 Tablets in 150 CC HDPE bottle

7. EVALUATION PARAMETERS

7.1 BLEND CHARACTERISTICS:

The characteristics of a tablet that make it a popular dosage form. E.g. compactness, physical stability, rapid production capability, chemical stability and efficacy are in general dictated primarily by the qualities of the granulation from which it is made. Basically stated, materials intended for compaction into a tablet must possess two characteristics - Fluidity and compressibility. To a great extent these properties are required by the compression machine design. Thus good flow properties are a prerequisite for the successful manufacture of tablets. It is a property of all powders to resist the differential movement between particles when subjected to external stresses. This resistance is due to the cohesive forces between the particles. Tablets require the flow of the correct weight of material into a specific volume, the behaviour of the material under pressure is important; and the wetting of the powder is also critical for granulation and subsequent disintegration and dissolution of the dosage form. The prepared granules the l were subjected to the following tests.

7.2 BULK DENSITY

Bulk density is defined as the mass of a powder divided by the bulk volume.

- **Procedure:**

Weighed quantity of blend was transferred into 100ml measuring cylinder without tapping. During transfer the volume occupied by granules was measured. Bulk density was measured by using formula.

$Pb=m/v_o$

Where;

Pb : Bulk Density

m : Mass of the blend

v_o : Untapped Volume

7.3 TAPPED DENSITY:

- **Procedure:**

Weighed quantity of blend was transferred into 100ml measuring cylinder, volume occupied by granules was noted down. Then cylinder was subjected to 500/750/and 1250 taps in tapped density tester. Volume variation was calculated by using formula.

$Pt = m/v_i$

Where;

Pt :Tapped Density

m = Mass of the blend.

v_i= Tapped volume.

7.4 COMPRESSIBILITY INDEX:

Compressibility is the ability of power to decrease in volume under pressure. Compressibility is a measure that obtained from density determination.

- **Procedure:**

Weighed quantity of blend was transferred to 100ml of measuring cylinder, volume occupied was noted down. Then cylinder was subjected to 500/750 and 1250 taps in tapped

density tester the difference between two taps should be less than 2%.The percentage of compressibility Index is calculated by using formula.

CI: (Pt-Pb/ Pt) ×100

Where;

CI: Compressibility index

Pt: Tapped Density

Pb: Bulk Density

7.5 HAUSNER'S RATIO:

It is measurement of frictional resistance of the drug. It was determined by the ratio of tapped density and bulk density.

Hausner's Ratio: Pt / Pb

Where;

Pt: Tapped Density

Pb: Bulk Density**.**

7.6 ANGLE OF REPOSE:

Angle of Repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

The angle of repose was calculated by using the formula given below.

$$\text{Angle of Repose } (\theta) = \text{Tan}^{-1} (h/r)$$

Where, h = height of pile

r = radius of the base of the pile

θ = angle of repose.

7.7 Effect of Angle of Repose, Compressibility index and Hausner's ratio on Flow property.

Table No: 6 Precompression property of tablet formulation

Flow property	Angle Of Repose	Compressibility index (%)	Hausner's Ratio
Excellent	25° - 30°	0-10	1.00 – 1.11
Good	31° – 35°	11-15	1.12 – 1.18
Fair - aid not needed	36° – 40°	16-20	1.19 – 1.25
Passable - may hang up	41° – 45°	21-25	1.26 – 1.34
Poor - must agitate	46° – 55°	26-31	1.35 – 1.45
Very poor – requires more agitation	56° – 65°	32-37	1.46 -1.59
Very very poor	>66°	>38	>1.6

7.8 SIEVE ANALYSIS:

The sieves are arranged according to the coarsest at the top and finest at the bottom. The weighed samples of granules are placed on the top sieve. After sieve shaker has completed for a predetermined period of time, the materials that have been sieved are collected to check their weight, the powder retained on each sieve is weighed and arithmetic mean of sample is determined.

7.9 GENERAL APPEARANCE:

The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, color, presence or absence of odor, taste etc.

7.9.1 SIZE & SHAPE:

It can be dimensionally described & controlled. The thickness of a tablet is onlyvariables. Tablet thickness can be measured by micro-meter or by other device. Tablet thickness should be controlled within a ± 5% variation of standard value.

The shape and dimensions of compressed tablets are determined by the type of tooling during the compression process. At a constant compressive load, tablets thickness varies with changes in die fill, particle size distribution and packing of the powder mix being compressed and with tablet weight, while with a constant die fill, thickness varies with variation in compressive load. Tablet thickness is consistent from batch to batch or within a batch only if the tablet granulation or powder blend is adequately consistent in particle size and particle size distribution, if the punch tooling is of consistent length, and if the tablet press is clean and in good working condition.

7.9.2 ORGANOLEPTIC PROPERTIES:

Colour is a vital means of identification for many pharmaceutical tablets and is also usually important for consumer acceptance. The color of the product must be uniform within a single tablet, from tablet to tablet and from lot to lot.

Odour may also be important for consumer acceptance of tablets. presence of an odor may be characteristic of the drug (e.g. vitamins), added ingredients (e.g. flavoring agent) or the dosage form (e.g. film-coated tablets).

Taste is also important for consumer acceptance of certain tablets (e.g. chewable tablets) and many companies utilize taste panels to judge the preference of different flavors and flavor levels in the development of a product. Taste preference is however subjective and the control of taste in the production of chewable tablets is usually based on the presence or absence of a specified taste.

7.10 WEIGHT VARIATION:

Composite samples of tablets (usually 10) are taken and weighed throughout the compression process. The composite weight divided by 10 which gives average weight but contain usual problems of averaged values. Within the composite sample that has an acceptable average weight, there could be tablets excessively over weight or underweight. To alleviate this problem British pharmacopeia provides limits for the permissible variations for uncoated and coated tablets:

Table No: 7 Weight variation tolerances for uncoated and film coated Tablets(USP)

Average weight of tablet (mg)	% Deviation
130 or Less	10
From 130 through 324	7.5
More than 324	5

7.11 CONTENT UNIFORMITY

The Content uniformity test is used to ensure that every tablet contain the amount of drug substance intended with little variation among tablets within a batch. Due to increased awareness of physiological availability, the content uniformity test has been included in the monographs of all coated and uncoated tablets and all capsules intended for oral administration where the range of size of the dosage form available include 50mg or smaller sizes.

7.12 THICKNESS AND DIAMETER:

The thickness and diameter of 10 tablets were recorded during the process of compression using Vernier caliper.

7.13 HARDNESS:

Tablets require a certain amount of strength or hardness and resistance to friability and withstand mechanical shocks of handling in packaging and shipping. In addition, tablets should be able to withstand reasonable abuse when in the hands of the consumer. Tablet hardness has been defined as force required to break a tablet in a diametric compression test. To perform this test, a tablet is placed between two anvils, force is applied to the anvils and the crushing strength

that just causes the tablet to break is recorded. Hardness is thus sometimes termed the tablet crushing strength.

Several devices operating in this manner have been and continue to be used to test tablet hardness: Monsanto tester, Strong-cobb tester, Pfizer tester, Erweka tester and Schleuniger tester.

7.14 FRIABILITY:

The laboratory friability tester is known as the Roche friabilator. It subjects a number of tablets to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25rpm dropping the tablets a distance of six inches with each revolution. Normally a pre weighed tablet sample is placed in the friabilator, which is then operated for 100 revolutions. The tablets are then dusted and reweighed. Some chewable tablets are most effervescence tablets undergo high friability weight losses, which accounts for the special stack packaging that may be required for these types of tablets. When capping is observed on friability testing, the tablet should not be considered for commercial use, regardless of the percentage of loss seen.

The percentage friability was determined by the formula:

$$\% \text{ friability} = W_1 - W_2 / W_1 \times 100$$

Where;

W_1 = Weight of tablets before test

W_2 = Weight of tablets after test

Limit: Not more than 1.0%

7.15 DISSOLUTION

Instruments Required:

i) Dissolution Apparatus.

ii) High performance liquid chromatography With CAD.

Dissolution Conditions:

Apparatus	:	Paddle
Medium	:	Milli- Q Water
Volume	:	900 mL
RPM	:	50
Temperature	:	37 ± 0.50 C
Time points	:	1, 2, 4, 6, 8, 12, 16& 150 RPM

Preparation of 0.2 M Ammonium Acetate:

Weighed and transfer 15.4g of Ammonium Acetate into 1000 mL volumetric flask. Dissolve and dilute volume with water, adjust pH to 4.0 with acetic acid.

Mobile Phase A : 100 % Acetonitrile

Mobile Phase B : 100 % Water.

Mobile Phase C : 0.2 M Ammonium Acetate Buffer.

Potassium Chloride Standard Preparation: (750 mg)

Weighed and transferred 42.0 of potassium chloride standard into 50 mL flask, added 30 ml dulcet and sonicate 5.0 mins and diluted volume with diluents. Filtered through 0.45 filtr.

Sample Preparation:

Switch on the dissolution apparatus and fill the washed bowls with 900 ml each of dissolution media.

Allow the dissolution medium to attain the temperature of 37 ° C +/0.50 C.

Place six tablets separately in six bowls and start the instrument.

After the specified time withdraw required quantity of sample from a zone midway between the surface of the dissolution medium and top of the rotating paddle not less than 1 cm from the vessel wall.

Filter the sample through 0.45 µ nylon membrane filter.

Discard the first few ml of filtrate.

Collect the filtrate, and use as sample solution.

Procedure:

Before starting the system equilibrate the column with gradient composition at least 2 Hours.

Inject gradient (1 injection), Blank (1 injection), 6 Standard preparation and check for system suitability parameters,

The% RSD for area response of 6 replicate injection should be not more than 5.0 %

Tailing factor for potassium standard peak should not be more than 2.0

If system suitability parameters pass inject sample preparation one injection into chromatograph.

Record the chromatograms.

Note: Calculate the sum area response of potassium and chloride peaks.

Calculation:

$$= \frac{AT}{AS} \times \frac{WS}{DS} \times \frac{DT}{1} \times \frac{P}{100} \times \frac{100}{LC}$$

Where,

AT : The sum Area of potassium and chloride peak from sample chromatogram.

As : The sum Area of potassium and chloride peak from standard chromatogram.

Ws : Weight of potassium chloride standard in mg.

Ds : Dilution of standard solution.

Dt : Dilution of sample solution.

P : Potency of potassium chloride standard

LC : Label claim of potassium chloride in mg per tablet.[6]

7.16 ASSAY :(BY HPLC)

Instruments Required:

i) High performance liquid chromatography With CAD.

Preparation of 0.2 M Ammonium Acetate:

Weighed and transfer 15.4g of Ammonium Acetate into 1000 ml volumetric flask. Dissolve and dilute volume with water, adjust PH to 4.0 with acetic acid.

Mobile Phase A : 100 % Acetonitrile

Mobile Phase B : 100 % Water.

Mobile Phase C : 0.2 M Ammonium Acetate Buffer.

Potassium chloride Standard preparation:

Weighed and transferred 42.0 mg of potassium chloride standard into 50 ml flask, added 30 ml diluent and sonicate 5.0 mins and diluted volume with diluent. Filtered Through 0.45 filter.

Sample preparation:

Weighed 20 tablets and determine the average weight .Weigh and transferred the powdered tablets equivalent to 210 mg into 250 ml flask , add 150 ml diluent, sonicate 40 mins with intermediate shaking and kept 15 minutes for settling down and make up volume with diluent, mixed well. Filtered through 0.45µ filter and inject.

Procedure:

Before starting the system equilibrate the column with gradient composition at least 2 Hours.

Inject gradient (1 injection), Blank (1 injection), 6 Standard preparation and check for system suitability parameters,

The% RSD for area response of 6 replicate injection should be not more than 5.0 %

Tailing factor for standard peak should not be more than 2.0

If system suitability parameters pass inject sample preparation one injection into chromatograph.

Record the chromatograms.

Note: Calculate the sum area response of potassium and chloride peaks.

Calculate assay content in % of potassium chloride per tablet, by using the following formula.

$$= \frac{AT}{AS} \times \frac{WS}{DS} \times \frac{DT}{1} \times \frac{P}{100} \times \frac{100}{LC} \times AW$$

Calculate assay content in mg of potassium chloride per tablet, by using the following formula.

$$\frac{\%\ \text{of potassium chloride tablet}}{100} \times LC$$

Where,

AT : The sum Area of potassium and chloride peak from sample chromatogram.

As : The sum Area of potassium and chloride peak from standard chromatogram.

Ws : Weight of potassium chloride standard in mg.

Ds : Dilution of standard solution.

Dt : Dilution of sample solution.

P : Potency of potassium chloride standard

LC : Label claim of potassium chloride in mg per tablet.[33]

8. FORMULATION TRIALS:

Table No: 8 Formula of potassium chloride Extended release tablets

S. No	Ingredients	Direct compression		Wet granulation				
		F1	F2	F3	F4	F5	F6	F7
		(mg/ tab)	(mg/ tab)	(mg/ tab)	(mg/ tab)	(mg/ tab)	(mg/ tab)	(mg/ tab)
1	Potassium chloride	750	750	750	750	750	750	750
2	Hydrogenated vegetable oil	230	230	220	220	150	150	150
3	Ethocel 100 FP	--	--	--	--	30	50	70
4	Ethocel 10 FP	--	--	--	--	15	15	15
5	Hydroxyl propyl cellulose	--	--	20	30	--	--	--
6	Isopropyl alcohol			Q.S	Q.S	Q.S	Q.S	Q.S
7	Colloidal silicon dioxide	5	10	5	5	10	10	10
8	Talc	5	10	5	5	5	5	5
9	Magnesium stearate	10	10	10	10	10	10	10
10	**Core Average weight**	1000	1010	1010	1020	970	990	1010
11	Opadry II yellow 854520112	--	30	30	30	30	30	30
12	**Coated Average weight**	--	1040	1040	1050	1000	1020	1040

9. RESULTS

9.1 Blend parameters:

Table No: 9 Blend parameters

S.No	Number of Formulation	LOD	Bulk density (gms/ml)	Tap density (gms/ml)	Compressibility index %	Hausner's ratio
1.	F1	---	0.781	0.937	16.59	1.198
2.	F2	---	0.810	0.967	16.31	1.193
3.	F3	1.33%	0.751	0.882	14.96	1.176
4.	F4	1.39%	0.732	0.833	12.16	1.137
5.	F5	1.56%	0.789	0.909	13.21	1.152
6.	F6	0.45%	0.750	0.857	12.50	1.142
7.	F7	0.06%	0.831	0.909	8.58	1.093

9.2 SIEVE ANALYSIS

% of granules retained

Table No: 10 % of granules retained in gm.

S.No	Mesh size	F1	F2	F3	F4	F5	F6	F7
1.	20#	2.50	3.34	9.32	10.24	11.32	8.82	11.15
2.	30#	3.96	3.76	10.62	11.98	12.94	11.55	13.45
3.	40#	4.38	4.72	9.59	10.76	11.31	10.22	11.81
4.	80#	36.43	34.58	48.81	43.41	49.26	50.98	48.46
5.	100#	16.22	20.22	5.96	4.81	4.48	4.02	5.89

9.3 AVERAGE WEIGHT:

Table No: 11 Average Weight in mg.

S.No	F1	F2	F3	F4	F5	F6	F7
1.	1000.5	1010	1035	1014	968	993	1009
2.	999.34	1009	1012	1020	975	990	1005
3.	998	1012	1011	1016	971	986	1011
4.	1003	1010	1005	1019	970	989	1011
5.	1000.23	1007.2	1010	1024	965	990	1010
6.	998.8	1013	1009	1021	968	992	1008
7.	999.11	1010	1010	1020	972	993	1014
8.	1000.24	1009	1008	1019	974	990	1010
9.	1002	1008	1011	1018	966	988	1007
10.	1001.21	1010	1006	1017	971	987	1014
Min	**998**	**1006**	**1005**	**1016**	**966**	**986**	**1005**
Max	**1003**	**1013**	**1011**	**1024**	**975**	**993**	**1014**

9.4 THICKNESS, HARDNESS AND FRIABILTY VALUES:

Table : 12 Post compression parameters

Name of the tests	F1	F2	F3	F4	F5	F6	F7
Thickness (mm)	5.75	5.78	6.25	6.30	6.85	6.58	7.15
Hardness (Newton)	40N	70N	75N	68N	100N	70N	68N
Friability (%)	1.11%	0.99%	0.7%	0.19%	0.17%	0.15%	0.13%

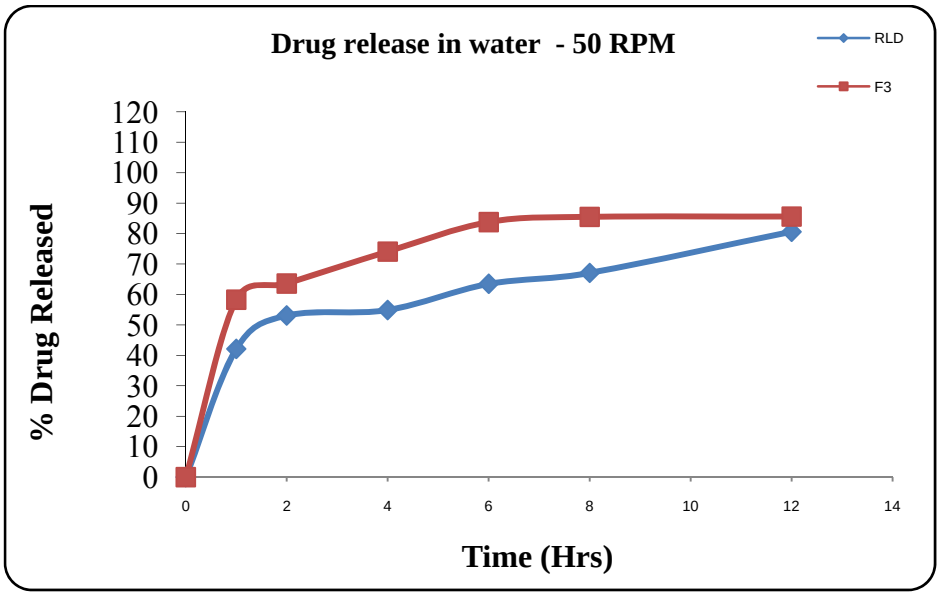
9.5 COMPARATIVE DISSOLUTION PROFILE (% DRUG RELEASE)

FORMULATION 3:

Table No: 13 Dissolution data for F3

Time intervals (hrs)	Reference	F3
1	42.1	58.3
2	53.1	63.6
4	54.9	74.1
6	63.5	83.8
8	67.1	85.5
12	80.6	85.6

Figure No: 6 Dissolution profile for referfence F3



F1 Value (Acceptance criteria 0-15) = 24.80

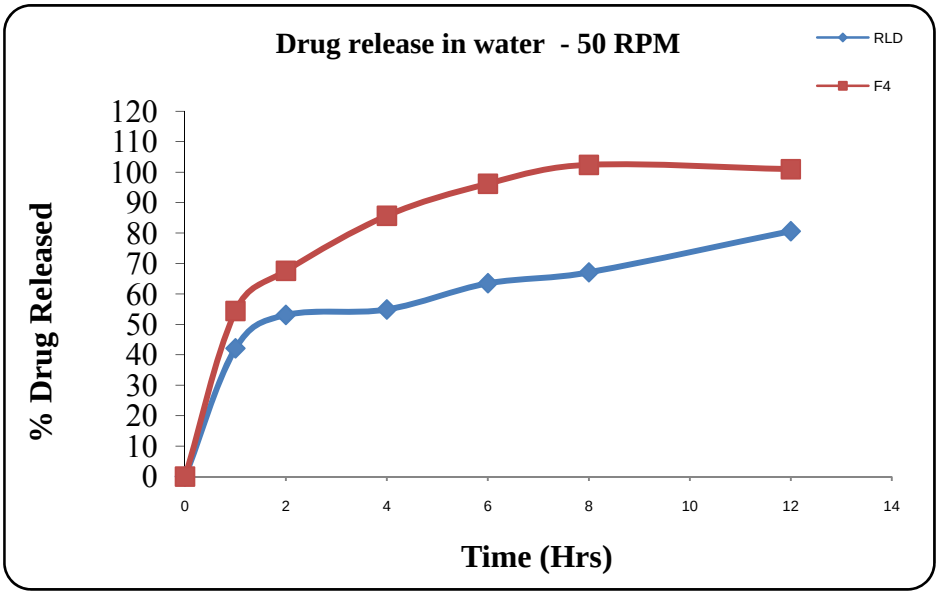
F2 Value (Acceptance criteria 50-100) = 40.07

Formulation 4:

Table No: 14 Dissolution data for F4

Time intervals (hrs)	(Reference)	F4
1	42.1	54.4
2	53.1	67.6
4	54.9	85.7
6	63.5	96.2
8	67.1	102.4
12	80.6	101.0

Figure No:7 Dissolution profile for referfence F4



F1 Value (Acceptance criteria 0-15) = 40.41

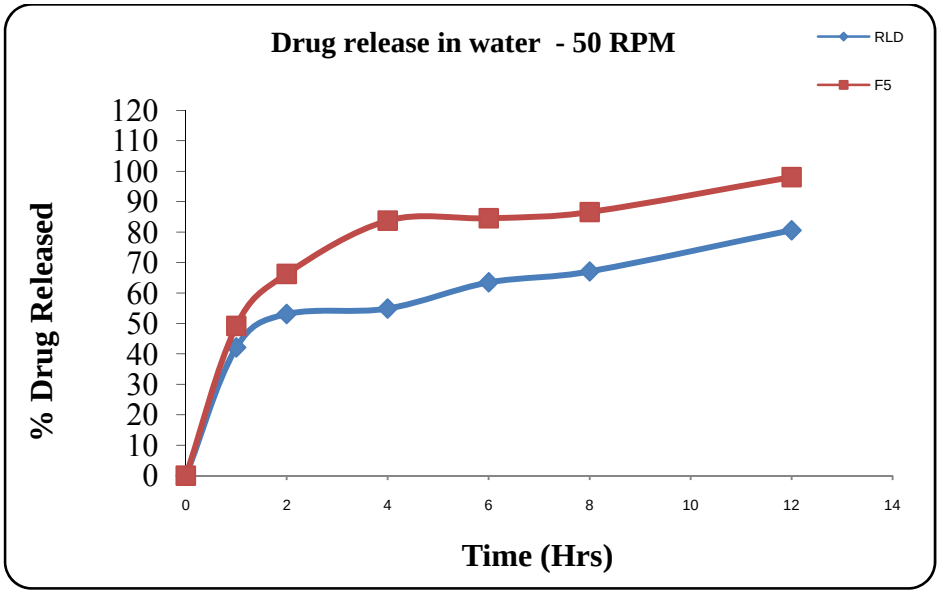
F2 Value (Acceptance criteria 50-100) =30.45

Formulation: 5

Table No: 15 Dissolution data for F5

Time intervals (hrs)	Reference	F5
1	42.1	49.2
2	53.1	66.3
4	54.9	83.8
6	63.5	84.6
8	67.1	86.6
12	80.6	98.1

Figure No: 8 Dissolution profile for referfence F5



F1 Value (Acceptance criteria 0-15) = 29.70

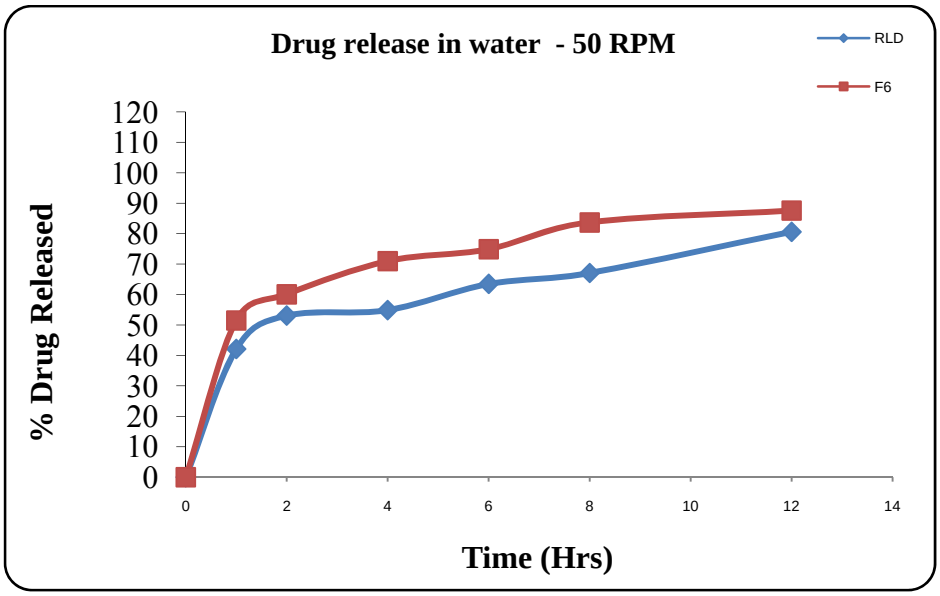
F2 Value (Acceptance criteria 50-100) = 37.53

Formulation 6:

Table No: 16 Dissolution data for F6

Time intervals (hrs)	Reference	F6
1	42.1	51.5
2	53.1	60.1
4	54.9	71.0
6	63.5	74.9
8	67.1	83.7
12	80.6	87.6

Figure No: 9 Dissolution profile for referfence F6



F1 Value (Acceptance criteria 0-15) = 18.68

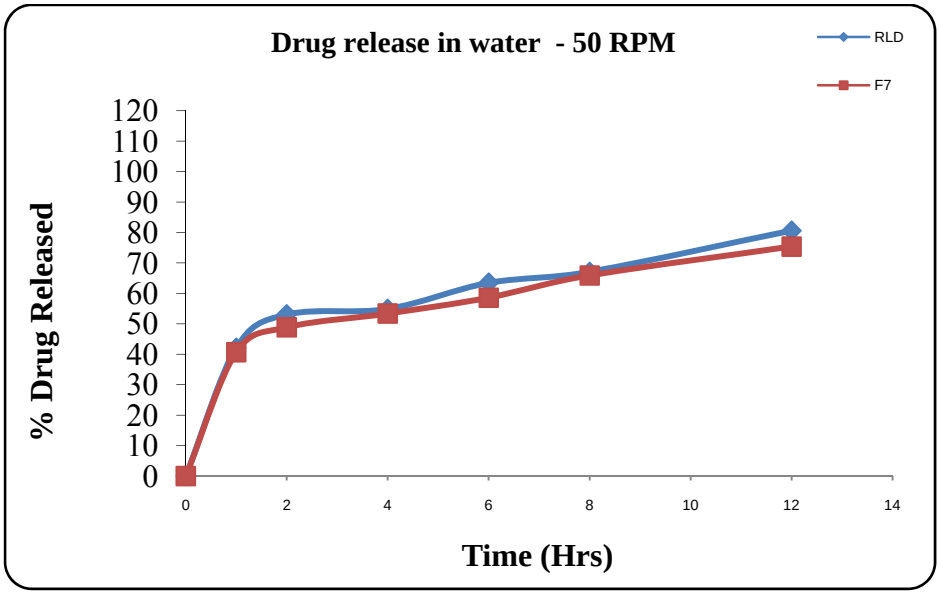
F2 Value (Acceptance criteria 50-100) = 46.77

Formulation: 7

Table No: 17 Dissolution data for F7

Time intervals (hrs)	Reference	F7
1	42.1	40.7
2	53.1	48.9
4	54.9	53.4
6	63.5	58.6
8	67.1	65.9
12	80.6	75.4

Figure No: 10 Dissolution profile for referfence F7



F1 Value (Acceptance criteria 0-15) = 5.09

F2 Value (Acceptance criteria 50-100) = 76.29

9.6 Assay:

Table No: 18 Assay values of formulation trials

Formulation no:	mg/tab	% release
F3	**750**	**99.7**
F4	**750**	**100.2**
F5	**750**	**101**
F6	**750**	**99.9**
F7	**750**	**100.3**

9.7 STABILITY DATA

Description:

Round shape yellow colour tablets, debossed with "KC10" were monitored under the Temperature and Relative humidity (40°C ± 2°C and 75% RH ± 5%).

Table No: 19 Stability Data

F7 Tests	Initial	One month
Assay	100.1 %	100 %
Dissolution at 2 hrs.	48.9 %	49.5 %
Water by KF	0.42 %	0.43 %

10. DISCUSSION

F1 & F2:

In the present study of potassium chloride extended release tablet were formulated by direct compression method, in these trials the blend parameters like bulk density, tapped density, compressibility index and Hausner's ratio showed poor flow property characteristics of blend. This was reflected in the compression as the tablets showed weight variation. During the compression lamination was observed at the hardness above 50N, weight variation observed, friability also more than the acceptance limit (1%), hence next trial is planned to perform with non-aqueous granulation to check the process feasibility.

F3

This trial was formulated by non-aqueous granulation method using of binder HPC(hydroxyl propyl cellulose).The blend parameters like bulk density, tapped density, compressibility index and Hausner's ratio showed passable flow property characteristics of blend. During the compression at above 100-110N lamination was observed, friability and lamination tendency was comparatively decreased than previous batch, during the film coating uniform distribution of film was not completely attained. Dissolution is faster than reference, Dissolution profile will not match with F1, F2 acceptance criteria. Hence it was suggested to increase the binder levels.

F4

The blend parameters like bulk density, tapped density, compressibility index and Hausner's ratio showed good flow property, But During the granulation in RMG some extent

over wetting was observed, during drying large lumps are not broken, Tablets parameter like thickness, hardness, friability, was found to be satisfactory., friability problem was significantly minimized, lamination was observed during the hardness testing of the tablets at above 90N. And indicating dissolution profile will not match with F1, F2 acceptance criteria. Dissolution is faster than reference, hence further trials were planned with Ethyl cellulose to control the release.

F5&F6

These trials were formulated by wet granulation method using ethyl cellulose 100cps 30mg/tab and 50mg/tab of respectively, Physical appearance of the tablets found to be satisfactory in both batches, Dissolution profile will not match with F1, F2 acceptance criteria. But the problem was significantly minimized, hence it was suggested to increase the polymers level.

F7

This trial was formulated by wet granulation method used ethyl cellulose 100 cps in 70mg/tab, The blend parameters like bulk density, tapped density, compressibility index and Hausner's ratio showed excellent flow property, Granules were compressed at a hardness of 65-70Newtons.Tablets parameter like thickness, hardness and friability, was found to be satisfactory, indicating drug release was similar to compared with reference product. Dissolution profile of this trial was within the F1, F2 acceptance criteria.

11. CONCLUSION

In the present study, Potassium chloride extended release tablets were prepared using non aqueous granulation method. Ethyl cellulose (Ethocel 100 FP) used as release controlling polymer, Ethyl cellulose (Ethocel 10 FP) used as a binder. Different level of Ethyl cellulose (Ethocel 100 FP) used in the development and F 7 experiment with Ethyl cellulose (Ethocel 100 FP) 70mg/tab was considered to the optimum since dissolution profile is comparable with reference product. F7 was located for stability, up to one month duration tablets were stable in 40°C ± 2°C 75% RH ± 5%, stability process still going on.

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